89. (New) The substantially purified non-human antibody of claim 88, wherein said antibody is at least 95% pure.

90. (New) The substantially purified non-human antibody of claim 89, wherein said antibody is at least 99% pure.

REMARKS

Claims 24-70 were pending in this application. Applicants note with appreciation that Groups I and III have been rejoined. Applicants also note with appreciation that claims 29-35 have been found to be free of art. In order to expedite the prosecution of the application and without conceding to the validity of any of the rejections, Applicants have canceled claims 48-52, without prejudice to Applicants' right to pursue the subject matter of the canceled claims in related applications. Applicants have also amended claims 24-26, 29, 55, 56 and 65 and added new claims 71-90. In view of the indication that dependent claims 30-32 would be allowable if rewritten in independent form, Applicants have combined claims 30-32 into independent new claim 71. A marked up version of amended claims 24-26, 29, 55, 56 and 65, with brackets indicating the deletions and underlining indicating additions, is attached hereto as Exhibit A. Amended claims 24-26, 29, 55, 56 and 65 and new claims 71-90 are fully supported by the instant specification, see, *e.g.*, page 10, line 22 to page 13, line 3 and page 70, line 10 to page 77, line 23 of the specification, and do not represent new subject matter. Claims 24-29, 33-47, and 53-90 are, therefore, pending in the application. A copy of the pending claims is attached hereto as Exhibit B.

The amendment and/or cancellation of claims has resulted in less than all of the originally named inventors being actual inventors of the invention presently being claimed. Thus, pursuant to 37 C.F.R. §1.48(b), the application has been amended to delete Martine Jandrot-Perrus and William Vainchenker as co-inventors of the application. This amendment is accompanied by a Petition For Correction of Inventorship Under 37 C.F.R. §1.48(b), accompanied by authorization of the fee required under 37 C.F.R. §1.17(i).

Applicants note the objection to the drawings for the reasons set forth in form PTO-948. In response, Applicants have enclosed herewith a Transmittal Of Formal Drawings and formal drawings 1-19.

The specification has been amended to reflect the drawing designations provided for in the formal drawings. These amendments have been made in order to conform to the current Patent Office regulations regarding formal drawings. The specification has also been amended to correct the instant applications's claim to priority. Specifically, the specification has been amended to reflect the fact that the instant application is a continuation-in-part of U.S. application Serial No. 09/345,468, filed June 30, 1999, which is a continuation-in-part of U.S. application Serail No. 09/454,824, filed on December 6, 1999. A marked up version of the paragraphs in the specification amended herein, with deletions and additions indicated by brackets and underlining, respectively, is attached hereto in Exhibit C. No new matter has been introduced by the amendments to the specification.

Applicants respectfully request that the amendments and remarks made herein be entered and fully considered.

1. THE REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, FOR LACK OF ENABLEMENT, SHOULD BE WITHDRAWN

Claims 29, 36-52, 54 and 57-70 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 29, 36-52, 54 and 57-70 are also rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner contends that the specification fails to provide enablement and written description support for a substantially purified antibody or fragment thereof which specifically binds to any extracellular domain of the amino acid sequence of SEQ ID NO:3 and kits or pharmaceutical compositions comprising such an antibody or fragment thereof.

The Examiner also contends that the specification fails to provide enablement and written description support for methods of making a substantially purified antibody or fragment thereof which specifically binds to the amino acid sequence of SEQ ID NO:3 comprising immunizing a mammal with a fragment of at least 15 amino acid residues of SEQ ID NO:3. The Examiner further contends that the specification fails to provide enablement and written description support for any antibody Fc region fusion polypeptide comprising an antibody Fc region linked to any fragment of at least 15 amino acid residues of the amino acid sequence of SEQ ID NO:3. For the reasons detailed below, Applicants respectfully assert that the rejections under 35 U.S.C. § 112, first paragraph, for lack of enablement and lack of written description support cannot stand and should be withdrawn.

In order to expedite the prosecution of the application and without conceding to the validity of the rejections, Applicants have canceled claims 48-52 without prejudice to Applicants' right to pursue the subject matter of the canceled claims in related applications.

Applicants have also amended claim 65 (and claims dependent therefrom) so that it no longer recites a method of making an antibody that specifically recognizes glycoprotein VI ("GPVI") comprising immunizing a mammal with a polypeptide comprising a fragment of at least 15 amino acid residues of the amino acid sequence of SEQ ID NO:3. Thus, presently pending claim 65 (and claims dependent therefrom) recites a method of making an antibody that specifically recognizes GPVI comprising: (1) immunizing a mammal with a polypeptide comprising the amino acid sequence of SEQ ID NO:3 or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with ATCC as Accession Number 207180; and (2) collecting a sample from the mammal containing an antibody that specifically recognizes GPVI.

Moreover, pending claim 29 recites a monoclonal antibody or fragment thereof which specifically binds to a polypeptide of the amino acid sequence of SEQ ID NO:3, or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with ATCC as Accession Number 207180. The Examiner acknowledges that the antibodies of claim 29, as amended, are enabled (*see, e.g.*, page 2, paragraph 7, item 2 of the Office Action).

With respect to the other claims rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement and written description, *i.e.*, claims 36-47, 54 and 57-70,

Applicants respectfully assert that the specification coupled with information well-known in the art as of the filing date of the instant application provides sufficient guidance to enable one of skill in the art to practice the presently claimed invention without undue experimentation. Applicants submit that methods for making antibodies, in particular monoclonal antibodies or fragments thereof, that specifically recognize/bind to human GPVI or an extracellular domain thereof, are described in the instant specification and were well-known in the art as of the filing date of the instant application. See, *e.g.*, the instant specification at page 69, line 23 to page 73, line 19. Second, methods for identifying antibodies that specifically bind to human GPVI (including an extracellular domain thereof) are described in the instant specification and were well-known as of the filing date of the instant application. See, *e.g.*, page 71, lines 1-13 of the instant specification.

The Examiner contends that polypeptides comprising an extracellular domain of SEQ ID NO:3 are not enabled or described because such polypeptides may differ in secondary structure from the native full length proteins. Applicants submit that antibodies directed to polypeptides comprising an extracellular domain of the amino acid sequence of SEQ ID NO:3 are fully described. Such antibodies recognize, *inter alia*, epitopes present in an extracellular domain of SEQ ID NO:3 having the structure of the native polypeptide. Alternatively, such antibodies can recognize denatured or partially denatured epitopes present in the primary structure of an extracellular domain of the amino acid sequence of SEQ ID NO:3, for example denatured or partially denatured epitopes present in amino acid residues 21 to 269 of SEQ ID NO:3, amino acid residues 48 to 88 of SEQ ID NO:3, or amino acid residues 134 to 180 of SEQ ID NO:3. Applicants submit that, given the state of the art of antibody production and the information provided in the specification, the structures of the claimed antibodies and of their epitopes are in full compliance with the written description requirements.

With respect to the enablement issue, Applicants submit that antibodies against polypeptides comprising an extracellular domain of SEQ ID NO:3 need not recognize the extracellular domain in its native conformation. Antibodies can readily be made against polypeptides comprising an extracellular domain of the amino acid sequence of SEQ ID NO:3 in denatured form (see, *e.g.*, the specification at page 69, lines 32-35). Such antibodies can be used for a number of purposes, including detection of a polypeptide

comprising an extracellular domain of the amino acid sequence of SEQ ID NO:3 on a Western blot. Additionally, Applicants submit that antibodies against polypeptides comprising an extracellular domain of the amino acid sequence of SEQ ID NO:3 can be made that recognize the native conformation of the extracellular domain of the amino acid sequence of SEQ ID NO:3. Such antibodies can be made, for example, by immunizing animals with eukaryotic cells that recombinantly express an extracellular domain of the amino acid sequence of SEQ ID NO:3, including but not limited to an extracellular domain of the amino acid sequence of SEQ ID NO:3 in the context of full length SEQ ID NO:3. Upon immunization of an animal with a eukaryotic cell that expresses an extracellular domain of the amino acid sequence of SEQ ID NO:3, the epitopes exposed to the immune system will be ones that exist on the cell surface, namely the extracellular portions of SEQ ID NO:3, thereby generating an immune response to and antibody production against the extracellular domain of the amino acid sequence of SEQ ID NO:3 expressed on the cell surface. Accordingly, antibodies that specifically bind to an extracellular domain of the amino acid sequence of SEQ ID NO:3 are fully enabled by the specification..

Applicants submit that none of the presently pending claims are directed to antibodies or methods of making antibodies which specifically bind to a polypeptide comprising any fragment of at least 15 amino acid residues of the amino acid sequence of SEQ ID NO:3., and that those rejections are thus moot. Applicants further respectfully assert that the specification coupled with information well-known in the art as of the filing date of the instant application provides sufficient guidance to enable one of skill in the art to practice the subject matter of the claims as amended herein without undue experimentation, and reasonably conveys to one of skill in the art that the Applicants were in possession of the claimed invention.

In view of the foregoing Applicants respectfully assert that the rejections under 35 U.S.C. § 112, first paragraph, for lack of enablement and lack of written description support cannot stand and should be withdrawn.

2. THE REJECTIONS UNDER 35 U.S.C. § 102(b) SHOULD BE WITHDRAWN

Claims 24-26, 36-40, 55, 61 and 62 are rejected under 35 U.S.C. § 102(b) as being anticipated by Sugiyama et al., 1987, Blood 69(6): 1712-1720 ("Sugiyama"). Claims

24-26, 36-40, 55, 61 and 62 are also rejected under 35 U.S.C. § 102(b) as being anticipated by Gibbins et al., 1997, FEBS Letters 413: 255-259 ("Gibbins"). The Examiner contends that Sugiyama teaches a composition comprising a substantially purified antibody, namely a human auto-antibody, and a $F(ab')_2$ fragment thereof that specifically binds to a collagen receptor with an apparent molecular weight of 62 KDa which is expressed by platelets. The Examiner contends that Gibbins teaches a composition comprising a substantially purified antibody, namely a human auto-antibody from a patient with autoimmune thrombocytopenia, and a $F(ab')_2$ fragment thereof that specifically binds to glycoprotein VI, a protein of approximately 60 KDa which is expressed by platelets. The Examiner contends that the collagen receptor to which antibodies described in Sugiyama and Gibbins bind appears to be the same as the amino acid sequence of SEQ ID NO:3 which is predicted to be approximately 62 KDa. The Examiner also contends that the antibodies described by Sugiyama and Gibbins bind to the platelet receptor that is expressed on the cell surface, and thus, the antibodies described by Sugiyama and Gibbins inherently bind to amino acid residues 21 to 269 of SEQ ID NO:3. For the reasons detailed below, Applicants respectfully assert that the rejections under 35 U.S.C. § 102 (b) cannot stand and should be withdrawn.

It is axiomatic that for a prior art reference to anticipate a claimed invention under 35 U.S.C. § 102, it has to meet every element of the claimed invention. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 U.S.P.Q. 81, 90 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987).

Neither Sugiyama nor Gibbins teach an antibody or a composition comprising an antibody or a fragment thereof which specifically binds to a polypeptide comprising the amino acid sequence of SEQ ID NO:3 or an extracellular domain thereof, or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with the ATCC as Accession Number 207180, wherein the antibody is substantially purified, as recited in claims 24, 26 and 36. As recited herein, the term "substantially purified" means that the antibody contains no more than 30% (by dry weight) of contaminating antibodies (Applicants direct the Examiner's attention to page 71, lines 13-18 of the specification for this definition).

Sugiyama describes the immunoprecipitation of a group of polypeptides, including a predominant 62 KDa (using reducing conditions) polypeptide and at least four other platelet polypeptides using bulk IgG obtained from a human patient with idiopathic

thrombocytopenic purpura. Sugiyama points out that the relationship, if any, between this group of polypeptides is unknown. Sugiyama also describes the ability of $F(ab')_2$ fragments produced from the human patient's bulk IgG to induce platelet aggregation and to inhibit platelet aggregation induced either by collagen or the patient's IgG. Sugiyama points out that it is unclear whether a single antibody or multiple antibodies with the patient's IgG mixture is/are responsible for the observed platelet aggregation activity. Gibbins uses the bulk human IgG mixture of Sugiyama and Fc receptor γ-chain ("FcR γ-chain") to demonstrate the constitutive association of GPVI with the FcR γ-chain. Gibbins also describes the tyrosine phosphorylation of the GPVI-associated FcR γ-chain and Syk in response to GPVI cross-linking mediated by $F(ab')_2$ fragments of the human bulk IgG preparation of Sugiyama. Thus, neither does Sugiyama or Gibbins teach a substantially purified antibody or a composition comprising a substantially purified antibody (as defined in the specification at page 71 and claimed herein) or a fragment thereof which specifically binds to GPVI or an extracellular domain thereof. Accordingly, neither Sugiyama nor Gibbins meet every element of the presently claimed invention, and therefore, do not anticipate the claimed invention.

In view of the foregoing, Applicants submit that the rejections under 35 U.S.C. §102(b) cannot stand and should be withdrawn.

3. THE REJECTION UNDER 35 U.S.C. § 103(a) SHOULD BE WITHDRAWN

Claims 36, 45-47, 54, 63 and 64 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Sugiyama or Gibbins each in view of Harlow et al., In: Antibodies a Laboratory Manual, 1988, Cold Spring Harbor Laboratory Publication, Cold Spring Harbor, NY, pages 321-358 ("Harlow") or U.S. Patent No. 5,877,289 to Thorpe et al. ("Thorpe"). The Examiner contends that: (a) Sugiyama teaches a composition comprising a substantially purified antibody, namely a human auto-antibody, and a $F(ab')_2$ fragment thereof that specifically binds to a collagen receptor with apparent molecular weight of 62 KDa which is expressed by platelets; (b) Gibbins teaches a composition comprising a substantially purified antibody, namely a human auto-antibody from a patient with autoimmune thrombocytopenia, and a $F(ab')_2$ fragment thereof that specifically binds to a glycoprotein VI, a protein of approximately 60 KDa which is expressed by platelets; (c) Harlow teaches methods of

labeling any antibody with a detectable substance; and (d) Thorpe teaches antibodies conjugated to a diagnostic agent or therapeutic agent and kits comprising antibodies conjugated to such agents. The Examiner concludes that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to link or conjugate the antibody taught by Sugiyama or Gibbins to a detectable substance or a therapeutic agent. The Examiner also concludes that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to produce kits comprising the antibody taught by Sugiyama or Gibbins conjugated to a detectable substance or a therapeutic agent. Applicants respectfully disagree.

To establish a *prima facie* case of obviousness, the teachings of the prior art must provide one of ordinary skill in the art with some suggestion or motivation to make the claimed composition. *In re Rijckaert*, 28 U.S.P.Q.2d 1955, 1956 (Fed. Cir. 1993). For a claimed invention to be deemed obvious in view of a prior art disclosure, the prior art disclosure must, firstly, give rise to a *suggestion of or motivation* for the claimed subject matter. Assuming such a suggestion or motivation is found, and the invention is thus arguably "obvious to try" to achieve, only then does one reaches the question of whether one of ordinary skill in the art would have had a reasonable expectation of success in achieving it. *See e.g.*, *In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991); *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). However, as discussed below, there is nothing in Sugiyama or Gibbins, individually or together with Harlow and Thorpe, that suggests or motivates the claimed invention.

As discussed above, neither Sugiyama nor Gibbins teach an antibody or a composition comprising an antibody or a fragment thereof which specifically binds to a polypeptide comprising an extracellular domain of the amino acid sequence of SEQ ID NO:3, wherein the antibody is substantially purified, *i.e.*, containing no more than 30% (by dry weight) of contaminating antibodies. Further, neither Sugiyama nor Gibbins suggests or provides any motivation, let alone a reasonable expectation of success, that such an antibody can be made. Accordingly, neither Sugiyama nor Gibbins, alone or in combination, renders obvious the claimed invention.

Neither Harlow nor Thorpe, alone or in combination, remedies the deficiencies of Sugiyama and Gibbins. Harlow teaches methods of detectably labeling an

antibody and Thorpe the conjugation of antibodies to a diagnostic or therapeutic agents. Neither Harlow nor Thorpe teaches, suggests or provides any motivation for the production of an antibody or a composition comprising an antibody or a fragment thereof which specifically binds to a polypeptide comprising an extracellular domain of the amino acid sequence of SEQ ID NO:3, wherein the antibody is substantially purified, *i.e.*, containing no more than 30% (by dry weight) of contaminating antibodies. Accordingly, the combination of Sugiyama, Gibbins, Harlow and Thorpe does not even rise to the level of suggesting or providing motivation the claimed invention. Thus, not even the threshold inquiry of the test for determining whether a claimed invention is obvious is met.

In view of the foregoing, Applicants submit that the rejection of claims 36, 45-47, 54, 63 and 64 under 35 U.S.C. §103(a) cannot stand and should be withdrawn.

CONCLUSION

Applicants respectfully request entry and consideration of the foregoing amendments and remarks. Applicants believe that all of the present claims meet all the requirements for patentability. Withdrawal of all rejections and reconsideration of the amended claims are requested. An allowance is earnestly sought.

Respectfully submitted,

Date September 26, 2002

Laura A. Coruzzi 30,742

Laura A. Coruzzi (Reg. No.)

By: Muna Abu-Shaar

Muna Abu-Shaar
Limited Recognition Under 37 C.F.R. § 10.9(b)
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Enclosure

EXHIBIT A
A MARKED UP VERSION OF THE CLAIMS AMENDED IN THE AMENDMENT FILED SEPTEMBER 26, 2002 IN U.S. APPLICATION SERIAL NO.: 09/503,387 ATTORNEY DOCKET NO.: 7853-178

24. (Amended) A composition [of substantially purified antibodies, or fragments thereof, which antibodies] comprising a substantially purified antibody or a fragment thereof that specifically [bind] binds to a polypeptide [comprising an] of the amino acid sequence of SEQ ID NO:3, or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with ATCC as Accession Number 207180.

25. (Amended) The [substantially purified antibody] composition of claim 24, wherein the [composition contains human antibodies] antibody is a human antibody.

26. (Amended) [An isolated] A substantially purified non-human antibody or fragment thereof which specifically binds to a polypeptide [comprising] of the amino acid sequence of SEQ ID NO:3, or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with ATCC as Accession Number 207180.

27. (Amended) [The antibody of claim 26 which is a] A substantially purified non-human monoclonal antibody or fragment thereof which specifically binds to a polypeptide of the amino acid sequence of SEQ ID NO:3, or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with ATCC as Accession Number 207180.

29. (Amended) A monoclonal antibody or fragment thereof which specifically binds to a polypeptide [comprising] of the amino acid sequence of SEQ ID NO:3, or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with ATCC as Accession Number 207180.

33. (Amended) A monoclonal antibody or fragment thereof which specifically binds to a polypeptide of the amino acid sequence of SEQ ID NO:3, or the amino acid

sequence encoded by the cDNA insert of the plasmid deposited with ATCC as Accession Number 207180, [The antibody of claim 29] which antibody is conjugated to a therapeutic moiety.

34. (Amended) A monoclonal antibody or fragment thereof which specifically binds to a polypeptide of the amino acid sequence of SEQ ID NO:3, or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with ATCC as Accession Number 207180, [The antibody of claim 29] which antibody is linked to a detectable substance.

55. (Amended) A pharmaceutical composition comprising [an antibody or fragment thereof as in] the composition of claim 24, 83, 84, 85 or 86, and a pharmaceutically acceptable carrier.

56. (Amended) A pharmaceutical composition comprising [an antibody, or fragment thereof, as in] the composition of claim 24, 83, 84, 85 or 86, a therapeutic moiety, and a pharmaceutically acceptable carrier.

65. (Amended) A method of making an antibody that specifically recognizes GPVI, the method comprising:

a) immunizing a mammal with a polypeptide comprising the amino acid sequence of SEQ ID NO:3, the amino acid sequence encoded by the cDNA insert of the plasmid deposited with ATCC as Accession Number 207180[, or a fragment of at least 15 amino acid residues of the amino acid sequence of SEQ ID NO:3]; and

b) collecting a sample from the mammal that contains an antibody that specifically recognizes GPVI.

EXHIBIT B
CLAIMS AS PENDING FOLLOWING ENTRY OF AMENDMENT OF SEPTEMBER 26, 2002
IN U.S. APPLICATION SERIAL NO.: 09/503,387
ATTORNEY DOCKET NO.: 7853-178

24. A composition comprising a substantially purified antibody or fragment thereof that specifically binds to a polypeptide of the amino acid sequence of SEQ ID NO:3, or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with ATCC as Accession Number 207180.

25. The composition of claim 24, wherein the antibody is a human antibody.

26. A substantially purified non-human antibody or fragment thereof which specifically binds to a polypeptide of the amino acid sequence of SEQ ID NO:3, or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with ATCC as Accession Number 207180.

27. A substantially purified non-human monoclonal antibody or fragment thereof which specifically binds to a polypeptide of the amino acid sequence of SEQ ID NO:3, or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with ATCC as Accession Number 207180.

28. The antibody of claim 27 which is a humanized antibody.

29. A monoclonal antibody or fragment thereof which specifically binds to a polypeptide of the amino acid sequence of SEQ ID NO:3, or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with ATCC as Accession Number 207180.

33. A monoclonal antibody or fragment thereof which specifically binds to a polypeptide of the amino acid sequence of SEQ ID NO:3, or the amino acid sequence

encoded by the cDNA insert of the plasmid deposited with ATCC as Accession Number 207180, which antibody is conjugated to a therapeutic moiety.

34. A monoclonal antibody or fragment thereof which specifically binds to a polypeptide of the amino acid sequence of SEQ ID NO:3, or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with ATCC as Accession Number 207180, which antibody is linked to a detectable substance.

35. The antibody of claim 34, wherein the detectable substance is selected from the group consisting of an enzyme, a prosthetic group, a fluorescent material, a luminescent material, a bioluminescent material, and a radioactive material.

36. A substantially purified antibody or a fragment thereof which specifically binds to an extracellular domain of the amino acid sequence of SEQ ID NO:3.

37. The antibody of claim 36, wherein the extracellular domain comprises amino acid residues 21 to 269 of SEQ ID NO:3.

38. The antibody of claim 36, wherein the extracellular domain comprises an immunoglobulin-like domain.

39. The antibody of claim 38, wherein the immunoglobulin-like domain comprises amino acid residues 48 to 88 or 134 to 180 of SEQ ID NO:3.

40. The antibody of claim 36 which is a polyclonal antibody.

41. The antibody of claim 36 which is a monoclonal antibody.

42. The antibody of claim 36 which is a chimeric antibody.

43. The antibody of claim 36 which is a humanized antibody.

44. The antibody of claim 36 which is a human antibody.

45. The antibody of claim 36 which is conjugated to a therapeutic moiety.

46. The antibody of claim 36 which is linked to a detectable substance.

47. The antibody of claim 46, wherein the detectable substance is selected from the group consisting of an enzyme, a prosthetic group, a fluorescent material, a luminescent material, a bioluminescent material, and a radioactive material.

53. A kit comprising an antibody or fragment thereof as in claim 34, and instructions for use.

54. A kit comprising an antibody or fragment thereof as in claim 46, and instructions for use.

55. A pharmaceutical composition comprising the composition of claim 24, 83, 84, 85, or 86, and a pharmaceutically acceptable carrier.

56. A pharmaceutical composition comprising the composition of claim 24, 83, 84, 85, or 86, a therapeutic moiety, and a pharmaceutically acceptable carrier.

57. A pharmaceutical composition comprising an antibody or fragment thereof as in claim 29, and a pharmaceutically acceptable carrier.

58. A pharmaceutical composition comprising an antibody or fragment thereof as in claim 29, a therapeutic moiety, and a pharmaceutically acceptable carrier.

59. A pharmaceutical composition comprising an antibody or fragment thereof as in claim 33, and a pharmaceutically acceptable carrier.

60. A pharmaceutical composition comprising an antibody or fragment thereof as in claim 33, a therapeutic moiety, and a pharmaceutically acceptable carrier.

61. A pharmaceutical composition comprising an antibody or fragment thereof as in claim 36, and a pharmaceutically acceptable carrier.

62. A pharmaceutical composition comprising an antibody or fragment thereof as in claim 36, a therapeutic moiety, and a pharmaceutically acceptable carrier.

63. A pharmaceutical composition comprising an antibody or fragment thereof as in claim 45, and a pharmaceutically acceptable carrier.

64. A pharmaceutical composition comprising an antibody or fragment thereof as in claim 45, a therapeutic moiety, and a pharmaceutically acceptable carrier.

65. A method of making an antibody that specifically recognizes GPVI, the method comprising:

a) immunizing a mammal with a polypeptide comprising the amino acid sequence of SEQ ID NO:3, the amino acid sequence encoded by the cDNA insert of the plasmid deposited with ATCC as Accession Number 207180; and

b) collecting a sample from the mammal that contains an antibody that specifically recognizes GPVI.

66. The method of claim 65 wherein the polypeptide is recombinantly produced.

67. The method of claim 65 which further comprises purifying antibodies from the sample.

68. The method of claim 65 which further comprises isolating a monoclonal antibody-producing cell from the mammal.

69. The method of claim 68 which further comprises collecting monoclonal antibodies which specifically recognize GPVI from the monoclonal antibody-producing cell.

70. The method of claim 65 wherein the antibody specifically binds to an extracellular domain of the amino acid sequence of SEQ ID NO:3.

71. A monoclonal antibody or fragment thereof which specifically binds to a polypeptide of the amino acid sequence of SEQ ID NO:3, or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with the ATCC as Accession Number 207180, wherein the antibody is a human, humanized or chimeric antibody.

72. The antibody of claim 71 which is conjugated to a therapeutic moiety.

73. The antibody of claim 71 which is linked to a detectable substance.

74. The antibody of claim 73, wherein the detectable substance is selected from the group consisting of an enzyme, a prosthetic group, a fluorescent material, a luminescent material, a bioluminescent material, and a radioactive material.

75. A kit comprising an antibody or fragment thereof as in claim 26, 87, 88, 89 or 90, and instructions for use.

76. A kit comprising an antibody or fragment thereof as in claim 27, and instructions for use.

77. A kit comprising an antibody or fragment thereof as in claim 29, and instructions for use.

78. A kit comprising an antibody or fragment thereof as in claim 71, and instructions for use.

79. A kit comprising an antibody or fragment thereof as in claim 73, and instructions for use.

80. A pharmaceutical composition comprising an antibody or fragment thereof as in claim 26, 87, 88, 89 or 90, and a pharmaceutical carrier.

81. A pharmaceutical composition comprising an antibody or fragment thereof as in claim 71, and a pharmaceutical carrier.

82. A pharmaceutical composition comprising an antibody or fragment thereof as in claim 72, and a pharmaceutical carrier.

83. The composition of claim 24, wherein said antibody represents at least 80% of total antibodies in the composition.

84. The composition of claim 83, wherein said antibody represents at least 90% of total antibodies in the composition.

85. The composition of claim 84, wherein said antibody represents at least 95% of total antibodies in the composition.

86. The composition of claim 85, wherein said antibody represents at least 99% of total antibodies in the composition.

87. The substantially purified non-human antibody of claim 26, wherein said antibody is at least 80% pure.

88. The substantially purified non-human antibody of claim 87, wherein said antibody is at least 90% pure.

89. The substantially purified non-human antibody of claim 88, wherein said antibody is at least 95% pure.

90. The substantially purified non-human antibody of claim 89, wherein said antibody is at least 99% pure.

EXHIBIT C
A MARKED UP VERSION OF THE PARAGRAPHS IN THE SPECIFICATION OF U.S. APPLICATION SERIAL NO. 09/503,387 AMENDED ON SEPTEMBER 26, 2002
ATTORNEY DOCKET NO.: 7853-178

On page 1, please amend the paragraph beginning on line 3 as follows:

This application is a continuation-in-part of U.S. Application Serial No. 09/454,824, filed December 6, 1999, which is a continuation-in-part of U.S. Application Serial No. [09/345,068] 09/345,468, filed June 30, 1999, now U.S. Patent No. 6,245,527, the entire disclosure of each [which] is incorporated herein by reference.

On page 13, please amend the paragraph beginning on line 29 as follows:

[FIGURE 1 depicts] FIGURES 1A-1B depict the cDNA sequence of human TANGO 268 (SEQ ID NO:1) and the predicted amino acid sequence of human TANGO 268 (SEQ ID NO:3). The open reading frame of SEQ ID NO:1 extends from nucleotide 36 to nucleotide 1052 of SEQ ID NO:1 (SEQ ID NO:2).

On page 14, please amend the paragraph beginning on line 5 as follows:

[FIGURE 3 depicts] FIGURES 3 depict an alignment of the nucleotide sequence of the open reading frame for human monocyte inhibitory receptor precursor (SEQ ID NO:24; GenBank Accession Number U91928) and the nucleotide sequence of the open reading frame for human TANGO 268 (SEQ ID NO:2). The nucleotide sequences of coding regions of human monocyte inhibitory receptor precursor and human TANGO 268 are 37.7% identical. The nucleotide sequences of full-length, including the 5' and 3' untranslated regions (UTRs), human monocyte inhibitory receptor precursor SEQ ID NO:11; GenBank Accession Number U91928) and human TANGO 268 are 49.9% identical. These alignments were performed using the ALIGN alignment program with a PAM120 scoring matrix, a gap length penalty of 12, and a gap penalty of 4.

On page 14, please amend the paragraph beginning on line 31 as follows:

FIGURE 6 depicts a cDNA sequence of mouse TANGO 268 (SEQ ID NO:14) and the predicted amino acid sequence of mouse TANGO 268 (SEQ ID NO:[15] 16). The open reading frame of SEQ ID NO:14 extends from nucleotide 63 to 1001 of SEQ ID NO:14 (SEQ ID NO:15).

On page 15, please amend the paragraph beginning on line 7 as follows:

[FIGURE 8 depicts] FIGURES 8A-8D depict an alignment of the nucleotide sequence of the open reading frame for human monocyte inhibitory receptor precursor (SEQ ID NO:24; GenBank Accession Number U91928) and the nucleotide sequence of the open reading frame for mouse TANGO 268 (SEQ ID NO:15). The nucleotide sequences of coding regions of human monocyte inhibitory receptor precursor and mouse TANGO 268 are 34.4% identical. The nucleotide sequences of full-length, including the 5' and 3' untranslated regions (UTRs), human monocyte inhibitory receptor precursor SEQ ID NO:11; GenBank Accession Number U91928) and mouse TANGO 268 are 35.6% identical. These alignments were performed using the ALIGN alignment program with a PAM120 scoring matrix, a gap length penalty of 12, and a gap penalty of 4.

On page 23, please amend the paragraph beginning on line 28 as follows:

A cDNA encoding human TANGO 268 was identified by analyzing the sequences of clones present in a human megakaryocyte cDNA library. This analysis led to the identification of a clone, jthea105e02, encoding full-length human TANGO 268. The human TANGO 268 cDNA of this clone is 2047 nucleotides long ([Figure 1] Figures 1A-1B; SEQ ID NO:1). The open reading frame of this cDNA, nucleotides 36 to 1052 of SEQ ID NO:1 (SEQ ID NO:2), encodes a 339 amino acid transmembrane protein ([Figure 1] Figures 1A-1B; SEQ ID NO:3) that, as discussed below, represents a platelet-expressed collagen receptor glycoprotein.

On page 26, please amend the paragraph beginning on line 1 as follows:

[Figure 3 shows] Figures 3A-3C show an alignment of the human TANGO 268 coding region (SEQ ID NO:2) with the human monocyte inhibitory receptor precursor protein coding region (SEQ ID NO:24). The human monocyte inhibitory receptor has been

shown to downregulate activation responses by phosphatases. The nucleotide sequences of coding regions of human monocyte inhibitory receptor precursor and human TANGO 268 are 37.7% identical. The full-length nucleic acid sequence of human TANGO 268 (SEQ ID NO:1) exhibits 49.9% identity to the full-length nucleic acid human monocyte inhibitory receptor precursor (SEQ ID NO:11; Accession Number U91928).

On page 29, please amend the paragraph beginning on line 1 as follows:

In general, mouse TANGO 268 has most homology to various members of the immunoglobulin superfamily that includes NK inhibitory and activating receptors and Fc receptors. The full-length nucleic acid sequence of mouse TANGO 268 exhibits 35.6% identity to the full-length nucleic acid human monocyte inhibitory receptor precursor (SEQ ID NO:11; Accession Number U91928). [Figure 8 shows] Figures 8A-8D show an alignment of the mouse TANGO 268 coding region (SEQ ID NO:15) with the human monocyte inhibitory receptor precursor protein coding region (SEQ ID NO:24). The nucleotide sequences of the coding regions of human monocyte inhibitory receptor precursor and mouse TANGO 268 are 34.4% identical. The nucleotide sequences of the full-length human monocyte inhibitory receptor precursor (SEQ ID NO:11; Accession Number U91928) and full-length mouse TANGO 268 (SEQ ID NO:14) are 35.6% identical. Figure 9 shows that there is an overall 20.3% identity between the mouse TANGO 268 amino acid sequence and the human monocyte inhibitory receptor protein amino acid sequence (SEQ ID NO:12; Accession Number U91928).

On page 34, please amend the paragraph beginning on line 30 as follows:

Human tissues were studied using Northern blot or RT-PCR analysis. Northern blots ([Fig. 4D] Fig. 14D) revealed no specific message in brain, heart, skeletal muscle, colon, thymus, spleen, kidney, liver, small intestine, placenta, lung or lymph nodes. A 2kb transcript was only observed in bone marrow and fetal liver. A signal was inconsistently observed with peripheral blood cells, probably due to platelet RNA contamination in some samples. Indeed, transcripts for platelet glycoprotein IIb (GPIIb), a platelet specific protein, were also detected in these positive samples.

On page 52, please amend the paragraph beginning on line 4 as follows:

TABLE 1: Summary of TANGO 268 Sequence Information

Gene	cDNA	ORF	Figure	Accession Number
Human TANGO 268	SEQ ID NO:1	SEQ ID NO:2	[Figure 1] Figures 1A-1B	207180
Mouse TANGO 268	SEQ ID NO:14	SEQ ID NO:15	Figure 6	PTA-225